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November 3, 1999

Paul E. Helliker
Director
Department of Pesticide Regulation
830 K Street
Sacramento, California 95814

Dear Mr. Helliker:

SUBJECT: Methyl Parathion

Enclosed for your action are the Scientific Review Panel's Findings on methyl parathion as adopted at our September 16, 1999 public meeting. As you will see, the Panel recommends methyl parathion should be listed as a toxic air contaminant. We also approved your Department's report: Evaluation of Methyl Parathion as a Toxic Air Contaminant, as representing current science associated with this pesticide.

At the meeting, the Panel had an excellent discussion with staff from DPR, ARB, OEHHA on the issue of pesticide prioritization and exposure/monitoring characterization. I will provide you with recommendations from the Panel following discussion at the next SRP meeting in November.

The Panel is encouraged by the completion of another pesticide and expects further progress with the current work on MITC, naled, molinate, and azinphos-methyl.

We trust our Findings and this transmittal letter will be made a part of the final report.

Sincerely,

John R. Froines

John R. Froines, Ph.D.
Chairman
Scientific Review Panel

Enclosure

cc: Scientific Review Panel Members
Mike Kenny, Executive Officer, ARB
Joan Denton, Ph.D., Director, OEHHA
Bill Lockett, Liaison, SRP

Findings of the Scientific Review Panel on
Evaluation of Methyl Parathion as a Toxic Air Contaminant
as adopted at the Panel's
September 16, 1999 Meeting

Pursuant to Food and Agricultural Code (FAC) sections 14022 and 14023, the Scientific Review Panel (SRP/Panel) has reviewed the report, *Evaluation of Methyl Parathion as a Toxic Air Contaminant* prepared by the Department of Pesticide Regulation (DPR) describing the public exposure to and health effects of, methyl parathion, taking into account its coexisting degradation product methyl paraoxon. The Panel members reviewed the public comments and the reviews of the Office of Environmental Health Hazard Assessment (OEHHA) and the Air Resources Board (ARB).

Furthermore, OEHHA has reviewed the report on the health effects of methyl parathion for the purposes of considering the identification of methyl parathion as a Toxic Air Contaminant (TAC). As part of its statutory responsibility, OEHHA has prepared findings on the health effects of methyl parathion which are to be included as part of the DPR report.

Based on the review and evaluation of methyl parathion, provided in the methyl parathion report, the Panel makes the following findings pursuant to FAC section 14023.

Environmental Fate and Exposure

1. From 1978 through 1993, the majority of methyl parathion used in California was applied to rice fields. These applications were seasonal, occurring over a 45-day period from Early-May through Mid-June, and localized, occurring in Colusa and Sutter Counties. These applications were made by fixed- and rotary-winged aircraft. A lesser but significant use of methyl parathion was to stone fruit and grape crops in Fresno and San Joaquin Counties. These applications were also made by aircraft or ground-based spray blower equipment. Methyl parathion applications to these crops were made over an eight-week period (May through June). Finally, methyl parathion applications were made to a variety of other crops (alfalfa, apples, cotton, small grains, sugar beet, and tomatoes). In total, approximately 80% of methyl parathion applications were made during April, May, June, and July of these years. The remaining 20% was applied during the rest of the year.

2. From 1994 through 1998, use patterns of methyl parathion changed. The majority of use shifted from rice to grapes and stone fruit crops (nectarine, peach, plum, and prune). During this period, applications to grapes averaged twelve percent and applications to stone fruits averaged 49% of the total methyl parathion applied. Applications to rice averaged only thirteen percent of the total methyl parathion applied. Again, methyl parathion's use remained seasonal with approximately 80% applied during April, May, June, and July. The remaining 20% was applied during the rest of the year.

3. In 1999 the United States Environmental Protection Agency, issued new use restrictions for methyl parathion. These restrictions:

   • Cancelled Children's Food Uses: All fruit (apples, peaches, pears, grapes, nectarines, cherries, and plums), carrots, succulent peas, succulent beans, and tomatoes.

   • Cancelled Other Food Uses: Artichokes, broccoli, Brussels sprouts, cauliflower, celery, collards, kale, kohlrabi, lettuce, mustard greens, rutabagas, spinach, and turnips.

   • Cancelled Non-Food Uses: Ornamentals, grasses grown for seed, mosquito use, and nursery stock.

   • Allow the Remaining Uses of Methyl Parathion: Alfalfa, almonds, barley, cabbage, corn, cotton, dried beans and peas, grass, hops, lentils, oats, onions, pecans, rapeseed, rice, rye, soybeans, sugar beets, sunflower, sweet potato, walnuts, wheat, and white potatoes.

4. From 1990 through 1998 methyl parathion applications in California ranged from 72,000 to 169,500 lbs Active Ingredient (AI). The greatest applications of methyl parathion occurred in Colusa, Fresno, San Joaquin, Sutter, and Tulare Counties, averaging 8,875, 20,000, 15,300, 10,500, and 19,500, pounds AI respectively.

5. In the environment, methyl parathion appears to be readily oxidized in the atmosphere to methyl paraoxon, which is more persistent in the atmosphere than methyl parathion. Methyl paraoxon is also the toxicologically active metabolite of methyl parathion in a biological system (See item 9 below). Therefore, human risk assessment of methyl parathion should take into account the concomitant exposure to both methyl parathion and methyl paraoxon in the environment.

6. DPR reviewed all available literature on ambient and application site air levels of methyl parathion. The most relevant monitoring study attempting to characterize the ambient air exposure was the study conducted in Colusa and Sutter Counties during the methyl parathion application season to rice (Seiber *et al.*, 1987). Rural ambient air levels of methyl parathion monitored at four locations ranged from non-detectable (detection limits 0.2 ng/m^3 or 0.02 ppt) to 34.7 ng/m^3 (3.2 ppt), corrected for trapping efficiency and limit storage recovery. The mean levels for the sampling locations ranged from 0.3 ng/m^3 (0.03 ppt) to 8.4 ng/m^3 (0.78 ppt). The highest levels of methyl parathion were detected in Colusa County.

The most relevant monitoring studies attempting to characterize the application site air exposures were conducted in Sutter (ARB, 1989) and in Glenn Counties (Seiber and McChesney, 1987). Application site air levels of methyl parathion ranged from 51 ng/m^3 (4.7 ppt) 48 hours after the application to 1,030 ng/m^3 (96.0 ppt) one hour after the application at 17 yards from the edge of the treated field.

7. The estimated rates of methyl parathion absorption through oral and inhalation routes are both 100%. The available data showed comparable toxicity between oral and inhalation routes based on dose per unit body weight.

Health Effects

8. Upon absorption, methyl parathion is metabolically activated to methyl paraoxon. Detoxification involved dealkylation and dearylation. Metabolites eliminated in the urine included *p*-nitrophenol, and other dealkylation and dearylation products (i.e., dimethyl phosphoric and phosphorothioic acid, desmethyl phosphate, desmethyl phosphorothioate, methyl phosphoric acid, phosphoric acid, and phosphate).

9. Methyl paraoxon inhibits cholinesterase (ChE) by binding to its active site. Inhibitions of plasma, red blood cell (RBC), and brain ChE are well documented. The consequences of accumulation of neurotransmitter, acetylcholine (ACh), at the nerve junctions are manifested in neurological signs and symptoms of both the peripheral and central nervous systems.

10. Age-specific and individual differential sensitivity to methyl parathion toxicity have been demonstrated. Young rats can be approximately 10-fold more sensitive than the adults to the acute toxicity of methyl parathion. The activities of paraoxonase, the enzyme that breaks down methyl paraoxon, can vary by more than 60-fold in humans, potentially resulting in significant variation in interindividual sensitivity.

Toxicities in humans

11. Acute (one to several days) and subchronic (several days to 3 months) exposures to methyl parathion result in measurable plasma and RBC ChE inhibition. The inhibition of brain ChE is evident in the cholinergic effects. Cholinergic effects reported in human acute poisoning cases are those typical of cholinergic over-stimulation, including salivation, lacrimation, miosis, defecation, urination, headache, dizziness, labored breathing, twitching, convulsions, and death.

12. Methyl parathion acute poisoning may also result in an intermediate syndrome (IMS) which typically appears 1 to 4 days after successful treatments of cholinergic crisis. Physical symptoms of IMS include muscle weakness, nerve palsy and may produce respiratory paralysis.

Toxicities in Animals

13. Acute (one to several days) and subchronic (14 days to 3 months) exposures to methyl parathion result in plasma, RBC, and brain ChE inhibition. Cholinergic effects commonly reported in animals include lacrimation, salivation, shivering, muscle fasciculation, and labored breathing. Neurobehavioral and neurohistopathological changes have also been reported.

14. Chronic (beyond 1 year) exposure to methyl parathion results in ChE inhibition (plasma, RBC, brain), tremors, alopecia, body weight changes, paralysis, and myelin degeneration of nerves.

15. Data showed that methyl parathion is genotoxic in laboratory studies. Long-term feeding studies in rats and mice did not show sufficient evidence of oncogenicity for a quantitative assessment of oncogenic risk, although some limited oncogenic evidence was indicated. The adequacy of rodent bioassays in detecting oncogenic potential is discussed.

16. Methyl parathion decreases the survival and body weight of rat pups in 2- and 3-generational reproductive toxicity studies and can cause male and female reproductive toxicities.

17. The developmental effects of methyl parathion include lower fetal body weight, increased resorption, reduced pup survival, and abnormalities and variations in fetal ossification in rats and rabbits. Neurobehavioral changes can result from *in utero* exposures.

18. Methyl parathion has not been shown to cause organophosphorus-induced delayed neuropathy (OPIDN) in hens.

19. Methyl parathion suppresses the immune system (e.g., lowered response of splenocyte antibody-forming cells, spleen, and thymus necrosis).

20. Methyl parathion causes hematological changes (decreased RBC, hemoglobin, and hematocrit).

21. Limited data suggest methyl parathion may disrupt endocrine function.

NOELs and Range of Risk to Humans

22. Out of the extensive toxicological database, a total of 41 datasets were selected as the most pertinent for collectively establishing the NOELs for characterizing the risk. The NOEL (No-Observed-Effect-Level) is the dose at which no effects are observed in a toxicity study. No inhalation studies are available for directly establishing the NOELs for inhalation exposures. Oral NOELs are used to assess the risk of inhalation exposures. Separate NOELs are determined for the following endpoints: plasma, RBC, and brain ChE inhibition, and overt toxicities. When the LOEL (Lowest-Observed-Effect-Level) is the lowest tested dose and is associated with a sensitive toxicity endpoint, a default factor of 10 is used to estimate a NOEL. This approach is used in estimating two subchronic NOELs (items 24-2 and 24-4 below) and one chronic NOEL (25-1 below) for use in risk characterization.

23. The report identifies two acute NOELs for risk assessment.

    1) A 30-day NOEL of 0.31 mg/kg/day is identified in humans based on plasma and RBC ChE inhibition.

    2) A NOEL of 0.025 mg/kg/day is determined in rats based on severe ChE inhibition (plasma, RBC, brain) and peripheral nerve demyelination at the LOEL of 7.5 mg/kg/day.

24. The report identifies four subchronic NOELs for risk assessment.

    1) A 30-day NOEL of 0.31 mg/kg/day identified in humans based on plasma and RBC ChE inhibition.

    2) An estimated NOEL of 0.003 mg/kg/day based on plasma ChE inhibition in dogs at a LOEL of 0.03 mg/kg/day.

    3) A NOEL of 0.029 mg/kg/day based on RBC ChE inhibition in rats at the LOEL of 0.29 mg/kg/day.

    4) An estimated NOEL of 0.02 mg/kg/day based on brain ChE inhibition and neurobehavioral effects in rats at a LOEL of 0.2-0.44 mg/kg/day.

25. The report identifies two chronic NOELs for risk assessment.

    1) An estimated NOEL of 0.01 mg/kg/day is based on RBC ChE inhibition in rats at the LOEL of 0.09 mg/kg/day.

2) A NOEL of 0.02 mg/kg/day is based on brain ChE inhibition, peripheral nerve degeneration, abnormal gait, and hematological alternations in rats at the LOEL of 0.2 mg/kg/day.

26. The report estimates that methyl paraoxon, which coexists with methyl parathion in the air, is approximately 10-fold more toxic than methyl parathion in rats. A Toxicity Equivalence Factor (TEF) of 10 for methyl paraoxon is used to estimate the total exposures to methyl parathion and methyl paraoxon and expressed in methyl parathion-equivalence.

27. The report estimates the high-end acute ambient air exposures at 0.065, 0.024, and 0.016 µg/kg/day for a child, an adult male, and an adult female, respectively. These are based on the 95th percentile of daily concentrations from the highest ambient monitoring site of rice application (Maxwell in Colusa County). The respective high-end seasonal (9-month) exposures for a child, an adult male, and an adult female are 0.02, 0.0075, and 0.0048 µg/kg/day. These are estimated based on the average daily concentrations over the monitoring period at the same site. The respective high-end chronic exposures for a child, an adult male, and an adult female are 0.015, 0.0056, and 0.0037 µg/kg/day. These are estimated as the 9-month exposure amortized over a year. Children (represented by 6-year olds) have higher breathing rates per body weight than adults, and hence, higher exposures.

28. The report estimates the exposure at application sites based on a 24-hour basis at 17 and 20 yards from the edge of the rice field. The respective exposures for a child, an adult male, and an adult female at 17 yards are 1.26, 0.48, and 0.31 µg/kg/day.

29. Risks of methyl parathion exposures are characterized as the margin of exposure (MOE) based on non-oncogenic effects. MOEs, the ratio of the NOELs to the exposure, were calculated based on very limited air monitoring data from rice field applications. The MOEs, ranging from children (lower value) to adults, are given below:

    1) The acute and subchronic MOEs based on plasma and RBC ChE inhibition in humans are 4,800 - 65,000.

    2) The acute MOEs based on ChE inhibition (plasma, RBC, brain) as well as peripheral nerve degeneration in rats are 390 - 1,600.

    3) The seasonal MOEs based on plasma ChE inhibition in dogs are 150 - 630.

    4) The seasonal MOEs based on RBC and brain ChE inhibition and nerve degeneration in rats are 1,000 - 6,000.

5) The chronic MOEs based on RBC ChE inhibition are 670 - 2,700.

6) The chronic MOEs based on brain ChE inhibition, nerve degeneration, abnormal gait, hematological effects in rats are 1,300 - 5,400.

30. The 24-hour MOEs at 17 and 20 yards from a rice application site are:

1) 250 - 1,000 based on plasma and RBC ChE inhibition in humans.

2) 20 - 80 based on ChE inhibition (plasma, RBC, brain) and peripheral nerve demyelination in rats.

31. The Reference Concentration (RfC) of methyl parathion in the air is calculated as the NOEL divided by an uncertainty factor (UF). A 100-fold UF is used when the NOEL is determined in animals. This accounts for the potentially higher sensitivity in humans as well as variability of sensitivity between humans. A 10-fold UF is used when the NOEL is determined in humans to account for the variability of response between humans. The calculation of reference concentration takes into account the concomitant presence of methyl paraoxon at approximately 25% of the level of methyl parathion.

32. The RfCs of methyl parathion calculated in the report are 0.1 $\mu g/m^3$ (10 ppt) for a 24-hour acute exposure and ranges from 0.01 - 0.08 $\mu g/m^3$ (1 - 8 ppt) for seasonal and chronic exposures.

Uncertainties or Other Relevant Information

33. Key uncertainties associated with the potential of oncogenicity to humans is the lack of sufficient evidence for a quantitative assessment of oncogenic risk although methyl parathion is genotoxic in laboratory studies, and there is limited evidence of oncogenicity in rodent bioassays.

33. Key uncertainties associated with the human acute and subchronic NOEL of 0.31 mg/kg/day include: the limited scope of observations and reporting, the small number of adult test subjects with unspecified body weight, and a substantial RBC ChE inhibition (55%) at the LOEL, which is only 10% higher than the NOEL. The potentially prolonged seasonal exposure (9-month) for methyl parathion casts further doubt about the adequacy of applying this threshold that was determined from a 30-day study.

35. Key uncertainties associated with the use of NOEL in animals are the interspecies extrapolations and that some of the NOELs are estimated from the LOELs. The use of NOEL determined in animals is necessary because they are based on endpoints insufficiently or not investigated in the human studies. A default 10-fold factor is used to

estimate a NOEL from the LOEL which represents the lowest dose tested. The following NOELs are thus estimated: subchronic NOEL of 0.003 mg/kg/day for plasma ChE inhibition in dogs, subchronic NOEL of 0.02 mg/kg/day for brain ChE inhibition and neurobehavioral effects in rats, and chronic NOEL of 0.01 mg/kg/day for RBC ChE inhibition in rats. The estimated subchronic NOEL of 0.02 mg/kg/day is supported by an established chronic NOEL at the same level and for similar effects. The potentially prolonged human seasonal exposure (9-month) also adds support to using the same level of NOEL for both seasonal and chronic exposures.

36 Key uncertainties in addressing the toxicities and exposures of methyl paraoxon include: the limited availability of data for a TEF determination, and the assumption of a fixed proportion between the levels of methyl parathion and methyl paraoxon in the air.

37. Key uncertainties associated with the exposure assessment include: the adequacy of point estimation approach to address the variations of human exposures, and the limited availability of monitoring data to identify the high end of exposures under all circumstances of use.

38 Under the 1996 Food Quality Protection Act, an additional safety factor of 10 would be used for protecting against the potentially higher sensitivity during pre- and/or post-natal periods. Applying this additional 10-fold factor will proportionally lower the RfCs previously listed in this findings document (item 32) to 0.01 $\mu g/m^3$ (1 ppt) for a 24-hour acute exposure and 0.001 - 0.008 $\mu g/m^3$ (0.1 - 0.8 ppt) for seasonal and chronic exposures.

39. In light of the important role of paraoxonase in the detoxification pathway, its wide polymorphic variations in human population points to the need for a continuing research on the interindividual variability of methyl parathion toxicity.

40. This assessment evaluates the risk of methyl parathion and methyl paraoxon in the air through the inhalation pathway. The agricultural use of methyl parathion is expected to result in significant exposures from additional pathways such as residues in food, and dermal exposures through occupational contacts.

41. The general patterns of pesticide use indicated the need to address the risk of concomitant exposure to other organophosphate chemicals through the same mechanism of toxicity. The multiple use of organophosphates is illustrated for Colusa County the air monitoring data of which are used in this document to model human exposures. Several organophosphates are used at a similar amount as methyl parathion and during the same methyl parathion air monitoring period (April - July) in Colusa County.

Conclusions

42. State regulations specify that if air concentrations for a pesticide exceed levels that would result in a ten-fold lower risk than a negligible risk shall be identified as toxic air contaminant. For non-oncogenic toxicity endpoints that are generally considered as having a threshold dose below which no effects are expected, a MOE of 100 is generally considered adequate for the protection of human health when the NOEL was determined in animals. Therefore, according to the criteria established in regulations, pesticides with MOEs less than 1,000 should be identified as a toxic air contaminant.

43. The MOEs for acute, subchronic, and chronic ambient air exposure are less than 1,000 for a child. The MOE for a 24-hour application site exposure is as low as 20 at 17 yards from a rice application site. Under this scenario, an exposure adjacent to the application site exceeding 30 minutes would result in a MOE below 1,000, the criterion for identifying a toxic air contaminant.

44. The Panel, after careful review of the draft version of the DPR report, *Evaluation of Methyl Parathion as a Toxic Air Contaminant*, as well as the scientific procedures and methods used to support the data, the data itself, and the conclusions and assessments on which the report is based, finds that this report is based upon sound scientific knowledge, methods, and practices and represents a balanced assessment of current scientific understanding.

45. For these reasons, we agree with the science presented in the report and recommend that the Director of DPR initiate regulatory steps to list methyl parathion as a toxic air contaminant pursuant to FAC section 14023(d) and the Code of California Regulations, Title 3, Section 6890(b).

I certify that the above are the
Findings adopted by the
Scientific Review Panel on September 16, 1999

John R. Froines

John R. Froines, Ph.D.
Chairman
Scientific Review Panel

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